PGRN-RIKEN-MA.27 Collaboration

Jim Ingle

for the

Mayo PGRN

Indiana PGRN

NCIC CTG

PGRN-TBCI Summit

March 31, 2008

PGRN-RIKEN-MA.27 Coalition Members

- Mayo PGRN
  - Dick Weinshilboum
  - Jim Ingle
  - Dan Schaid
  - Matt Ellis
- Indiana PGRN
  - Dave Flockhart
  - Vered Stearns
- NCIC CTG
  - Joe Pater
  - Judy-Anne Chapman
  - Kathy Pritchard
  - Cathy Elliott
  - Paul Goss
- RIKEN
  - Yusuke Nakamura
  - Taisei Mushiroda

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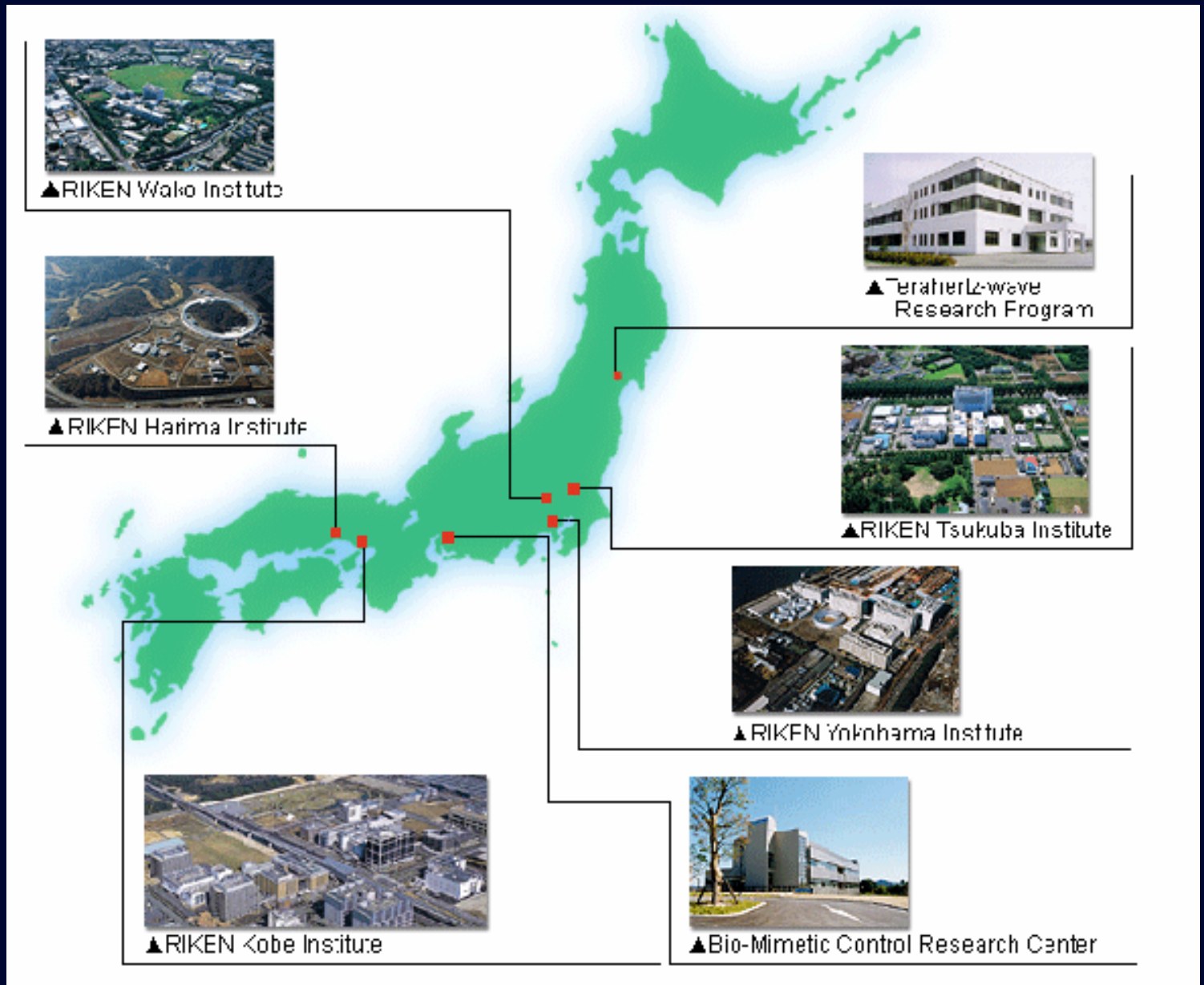
RIKEN (Rikagaku Kenkyūsho (理化学研究所)



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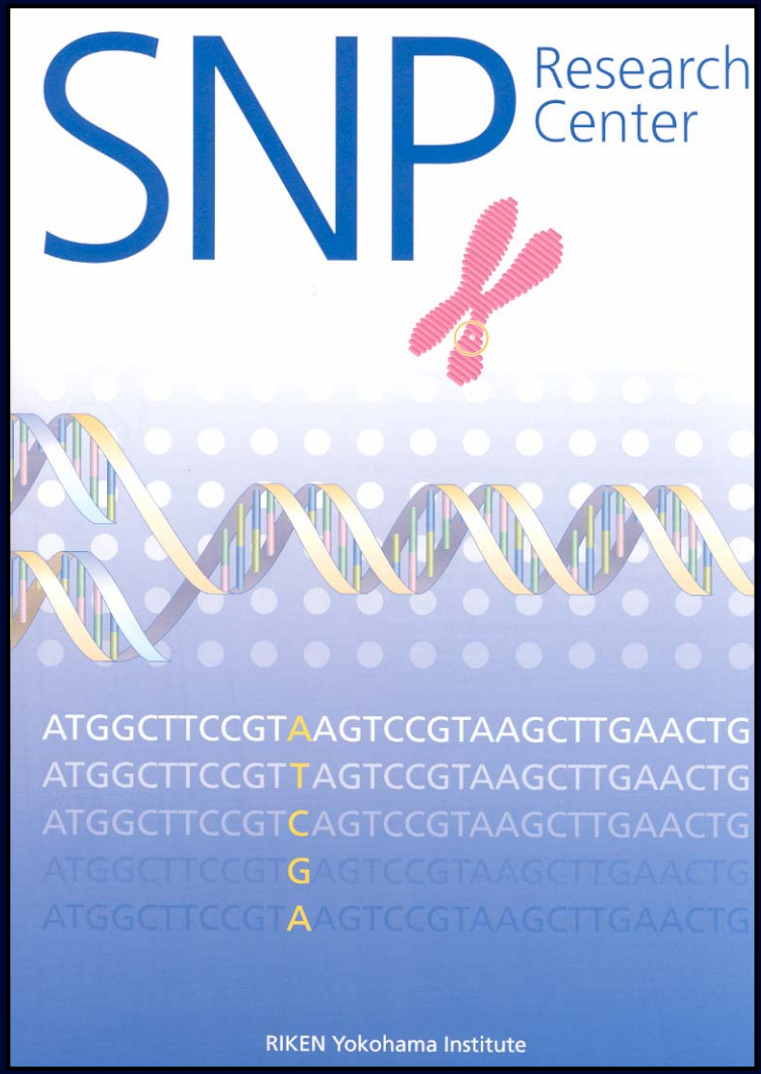
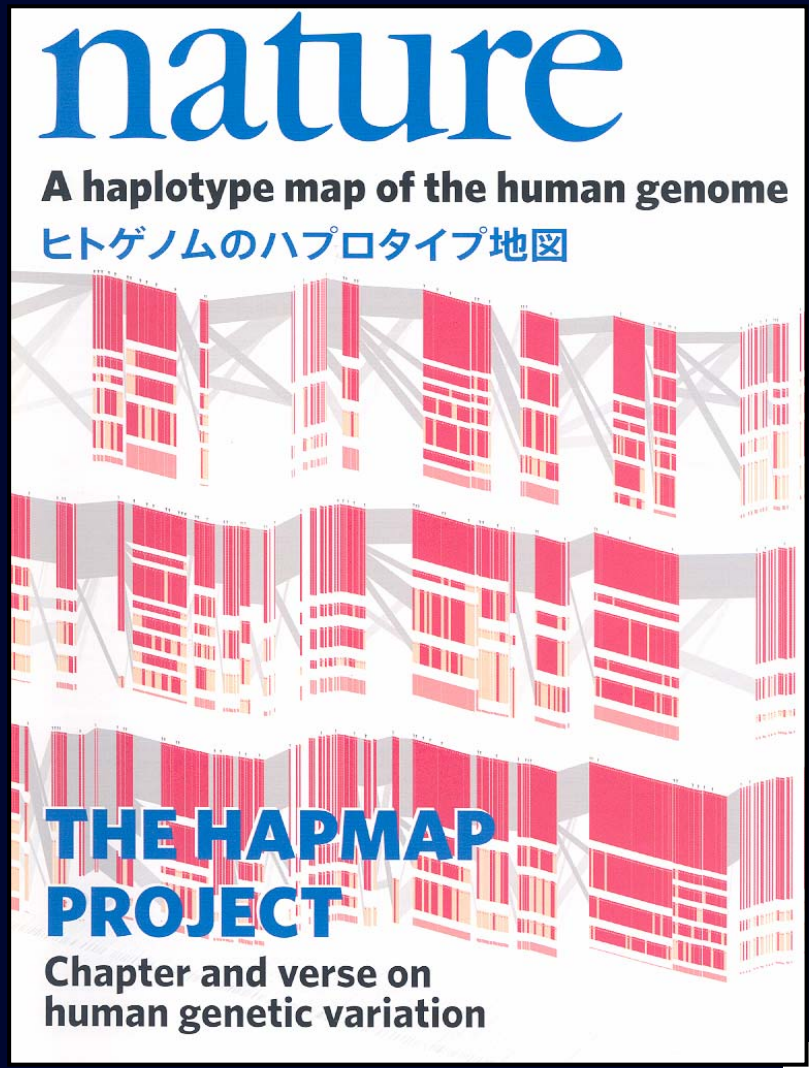
RIKEN SNP Research Center





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Aromatase Inhibitor Pharmacogenomics

PGRN Proposal to RIKEN:

Create a collaboration between RIKEN and the NIH-sponsored PGRN to perform GWASs using the NCI AI trial MA.27 to complement and extend a PGRN multi-institution GWAS study of anastrozole pharmacogenomics in order to encompass clinically relevant phenotypes

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A Randomized Phase III Trial of Exemestane Versus Anastrozole in Postmenopausal Women with Receptor Positive Primary Breast Cancer

The Breast Cancer Intergroup of North America

MA.27 / IBCSG 30-04
NCIC CTG / CTSU / IBCSG

Study Chair: Paul Goss
Study Co-Chairs:
George Sledge (ECOG) James Ingle (NCCTG)
Tom Budd (SWOG) Matt Ellis (CALGB)
Manuela Rabaglio (IBCSG)
Joe Pater (NCIC CTG Physician Coordinator)

MA.27
Resected Early Stage Breast Cancer
NCIC CTG ; NCCTG ; CALGB ; SWOG ; ECOG; IBCSG

n = 7520

postmenopausal receptor-positive women

RANDOMIZATION

Exemestane

Once daily x 5 Yrs

Anastrozole

Once daily x 5 Yrs

Treatment is for 5 years or until recurrence / second malignancy is documented

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MA.27 Current Status

- Activated June 2003
- Current accrual 7469
- Target accrual: 7520 (remains open to complete accrual to Bone and Breast Density sub-studies)
- Median follow-up: 2.0 years
- Biospecimens collection

  Blood for DNA: 5299

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PGRN-RIKEN Discussions

- Perform 2 genome wide association studies in collaboration with RIKEN on patients from MA.27 utilizing as phenotypes
  - Breast cancer events
  - Adverse events

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MA.27 GWAS
Disease Recurrence
Power Calculations

- Case Control: Estimate 600 patients with a breast cancer event by the end of 2009 plus 1200 matched controls (without event)

Frequency of carrying the risk allele

Odds Ratio	5%	10%	20%	50%
1.50	12%	32%	63%	82%
2.00	66%	95%	100%	100%

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MA.27
Adverse Events

- Musculoskeletal events
  - Grade 3, 4: 350
  - Grade 2 and a few grade 1 who went off treatment for this toxicity: 219

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MA.27 GWAS
Grade 3 and 4 Musculoskeletal AEs

Power Calculations

- Case Control: 1 patient with 2 controls

Frequency of carrying the risk allele

Odds Ratio	5%	10%	20%
2.5	0.05	0.38	0.86
3.0	0.23	0.82	0.99
4.0	0.83	0.99	1.00

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Final Agreement

- Start with a GWAS examining grade 3 and 4 musculoskeletal events during the fiscal year beginning April 1, 2008

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Current Status

- Developing letter of intent for submission to Correlative Sciences Committee of TBCI (goal: April)
- Fortnightly teleconferences of the Coalition.
  - Finalizing design
  - Finalizing cases and controls
- Ongoing communications with RIKEN

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Mayo PGRN and NCCTG

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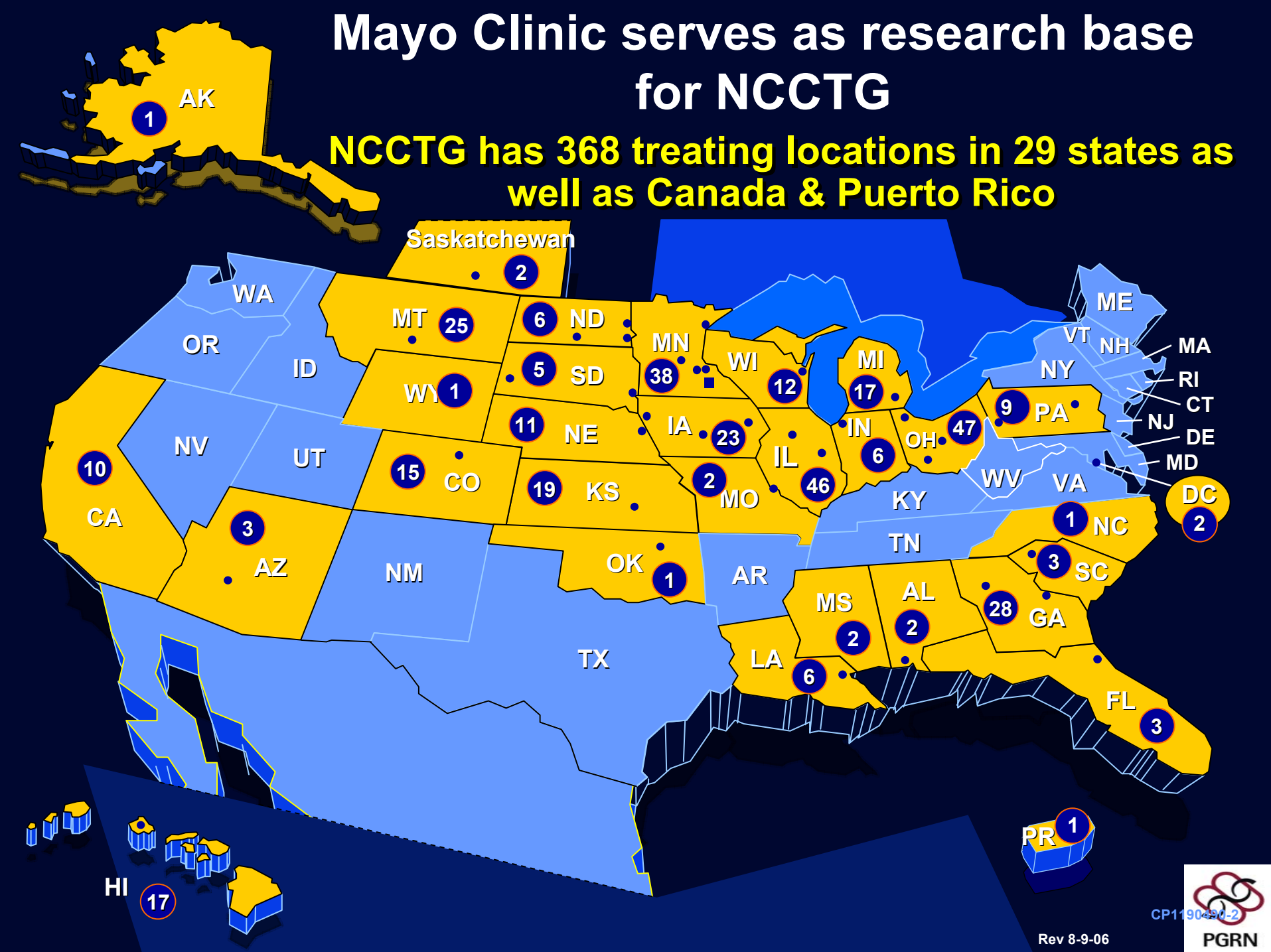
Mayo Clinic serves as research base for NCCTG

NCCTG has 368 treating locations in 29 states as well as Canada & Puerto Rico



Mayo PGRN-NCCTG Genomics Consortium

Steering Committee

James N. Ingle, MD
Director, Mayo Breast SPORE

Edith A. Perez, MD
Chair, NCCTG Breast Committee

Richard M. Weinshilboum, MD
PI, Mayo PGRN

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Mayo PGRN-NCCTG Genomics Consortium

Areas of Laboratory Research

- Tamoxifen
- Taxanes
- Anthracyclines
- Trastuzumab
- Gemcitabine
- Cyclophosphamide
- Lapatinib
- Platin drugs

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Human Variation Panel Cell Lines

- Genome-wide SNP data
  1 million SNPs/cell line
- Expression array data
  54,000 probe sets/cell line
- Exon array data
  1.4 million probe sets/cell line
- 2.5 million genomic data points/cell line
- 720,000,000 genomic data points total for 288 cell lines in every experiment

96 CA Cell Lines

96 HCA Cell Lines

96 AA Cell Lines

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Gemcitabine

- Gemcitabine is widely used to treat solid tumors including pancreatic cancer, ovarian cancer, breast cancer and nonsmall cell lung cancer
- Response varies widely
- Major side effects include GI side effects, neutropenia and thrombocytopenia

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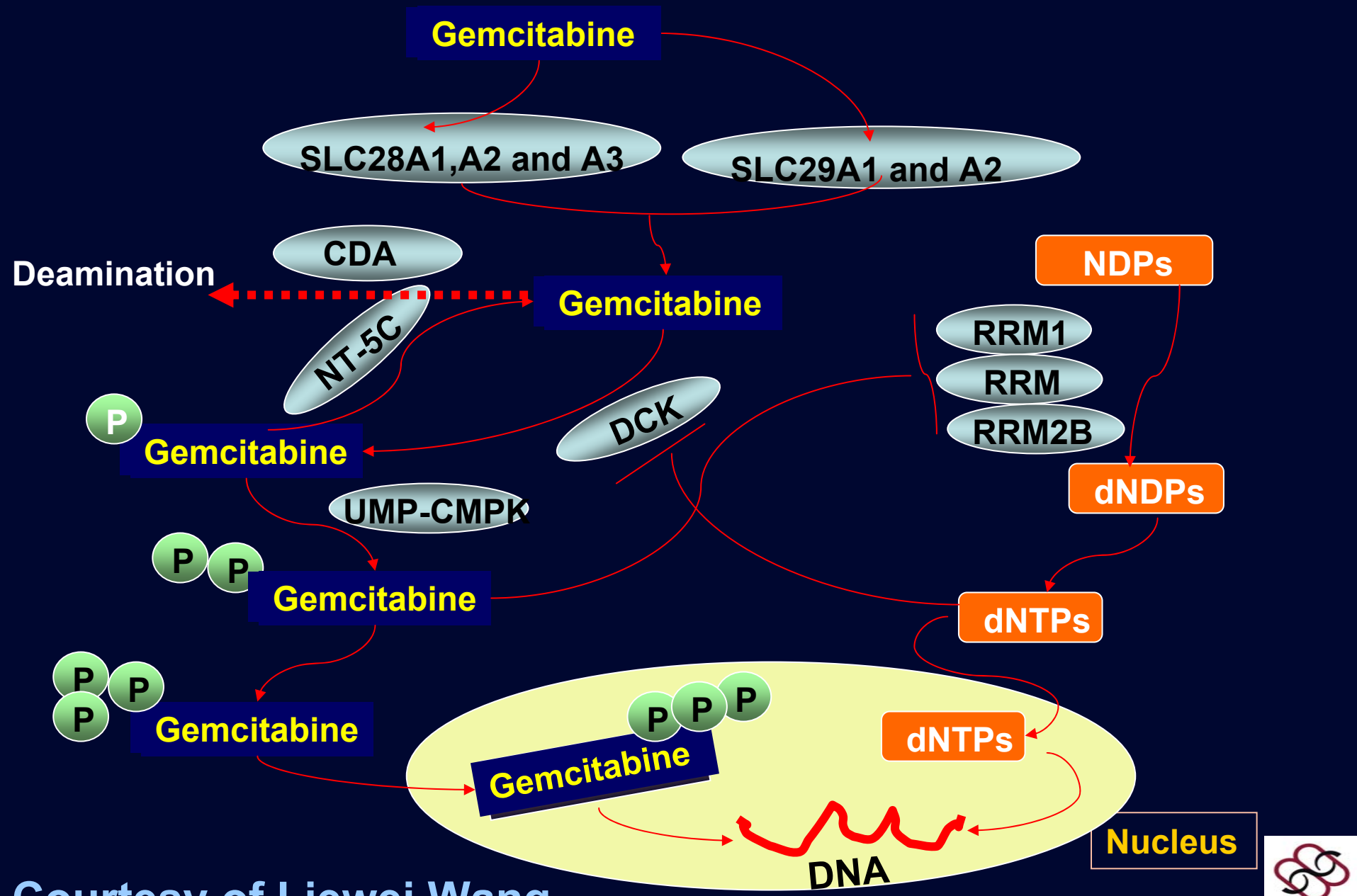
Gemcitabine Metabolic Pathway



Courtesy of Liewei Wang

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Hypothesis

Variation in gene expression across the genome might influence the response to gemcitabine

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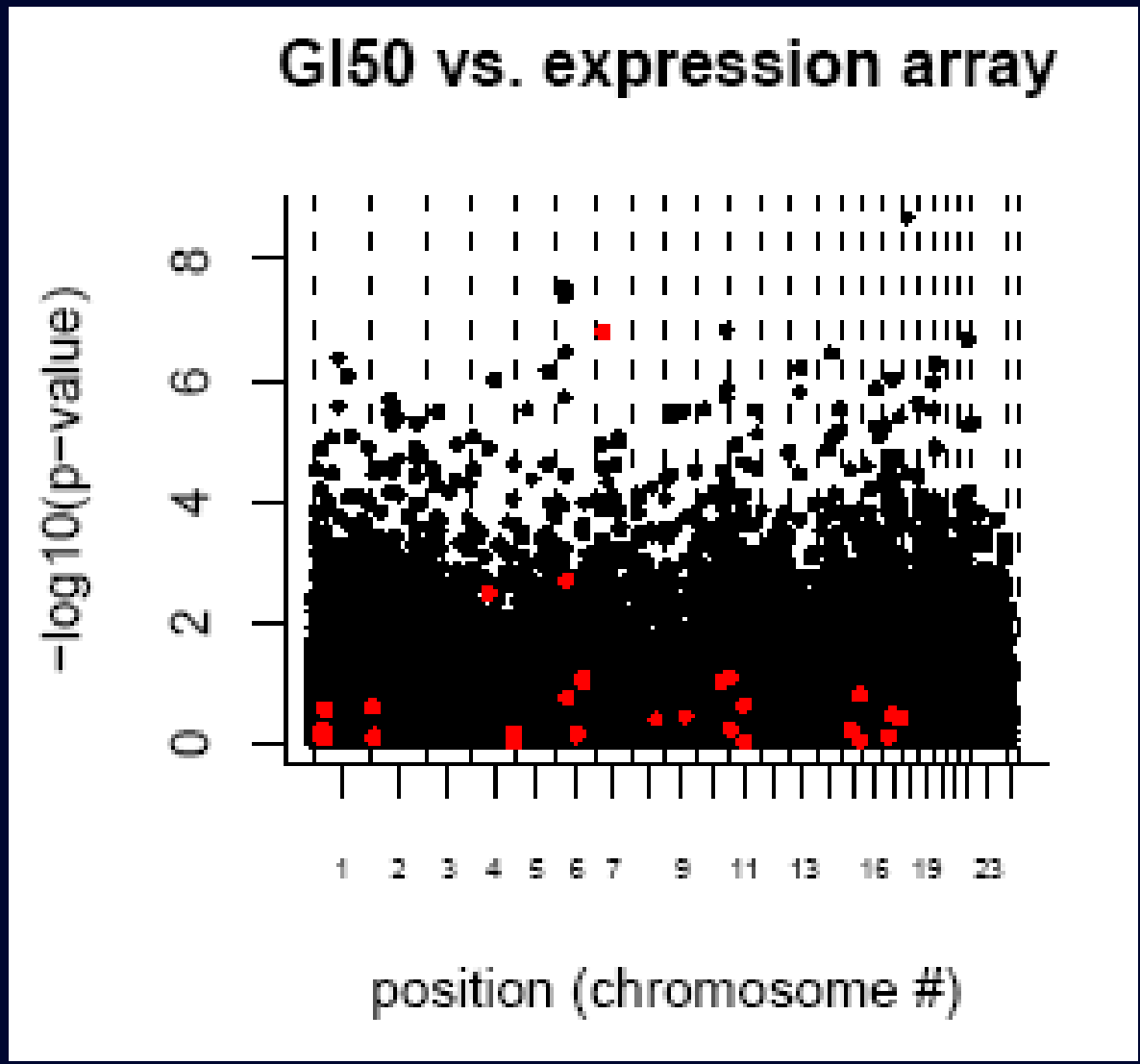
Gemcitabine Cytotoxicity and Variation in Gene Expression



Liewei Wang (under review)

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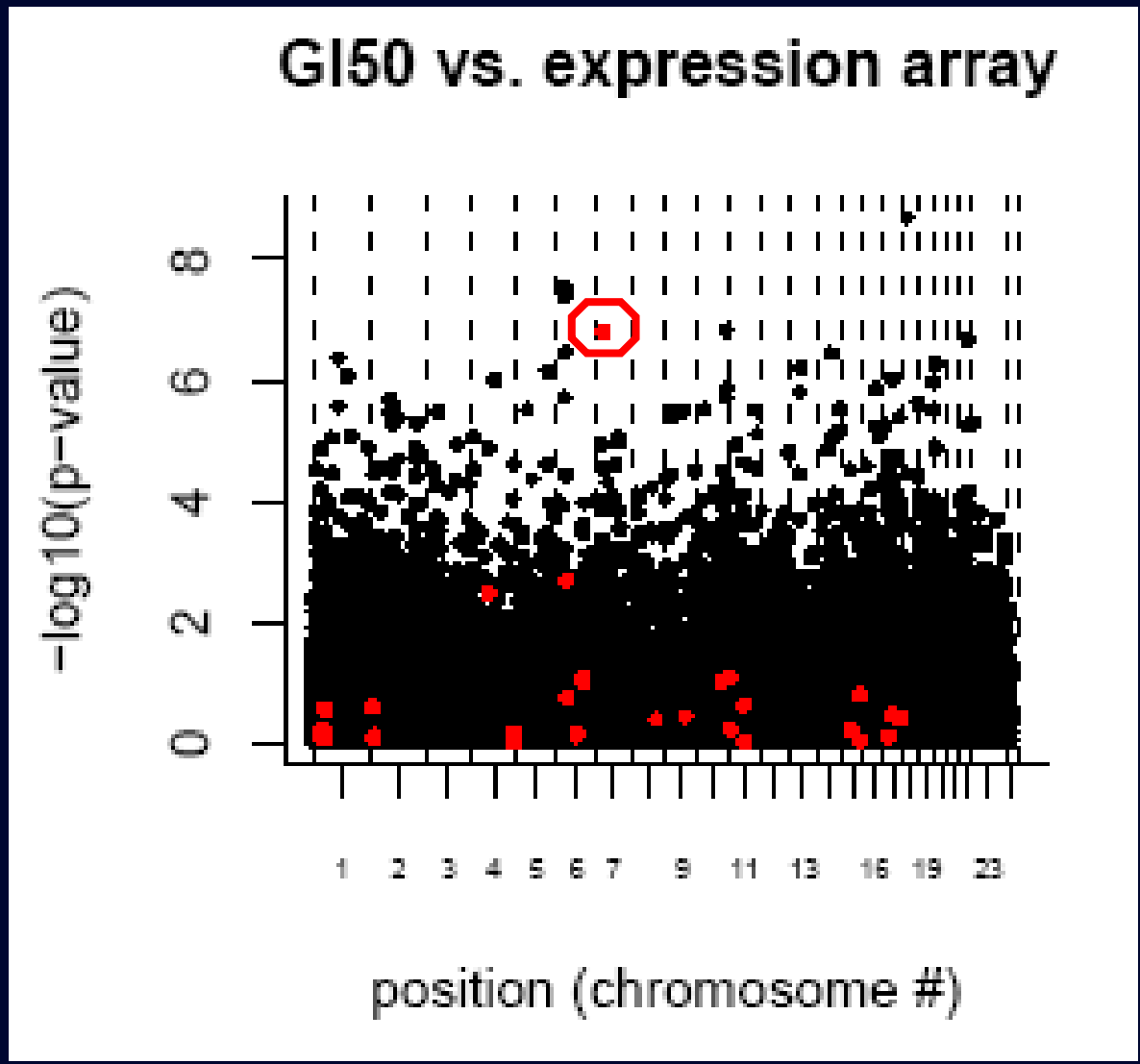
Gemcitabine Cytotoxicity and Variation in Gene Expression



Liewei Wang (under review)

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Clinical Trials

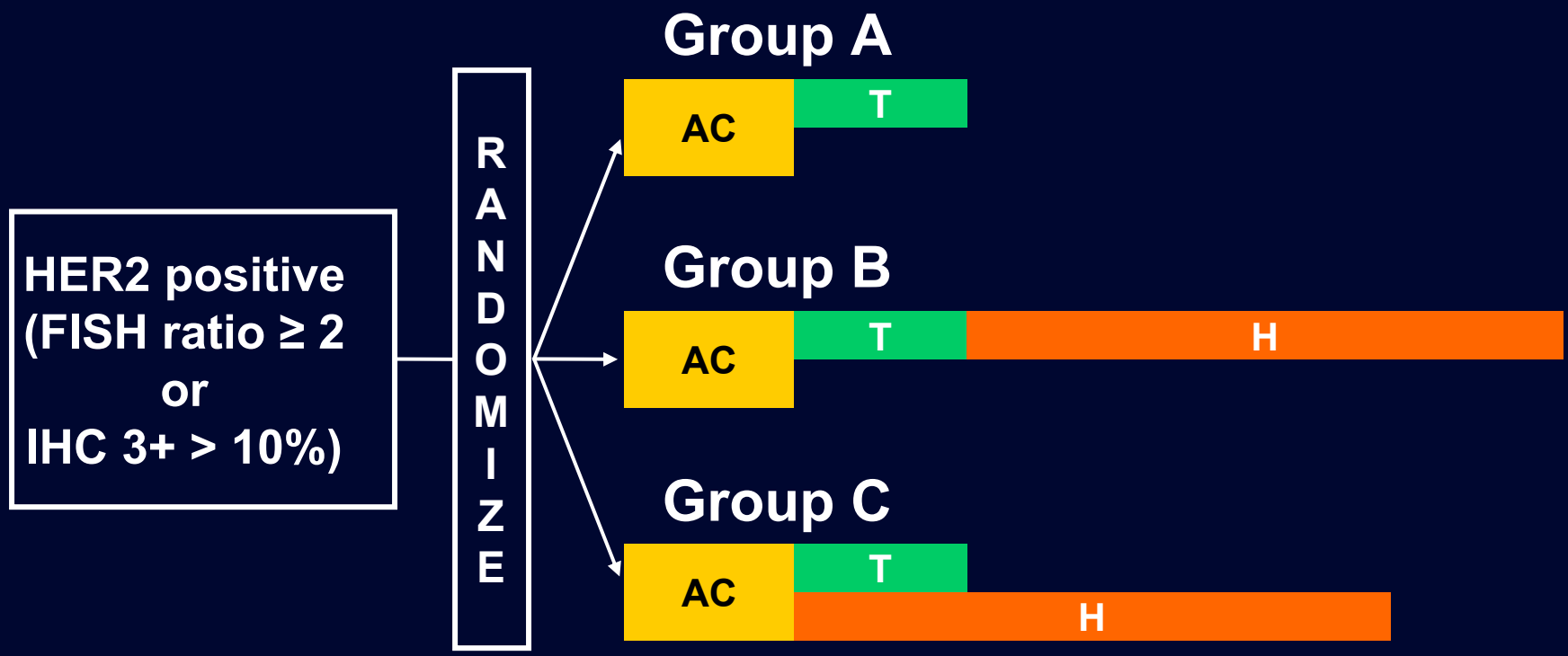
N9831

ALTTO

Others

NCCTG N9831 Trial Incorporating Trastuzumab in Adjuvant Therapy

n=3,505



= AC (**doxorubicin/cyclophosphamide** 60/600 mg/m^2 q3w × 4)

= T (**paclitaxel** 80 mg/m^2/wk × 12)

= H (**trastuzumab** 4 mg/kg loading + 2 mg/kg/wk × 51)

Perez EA. Protocol NCCTG-N9831

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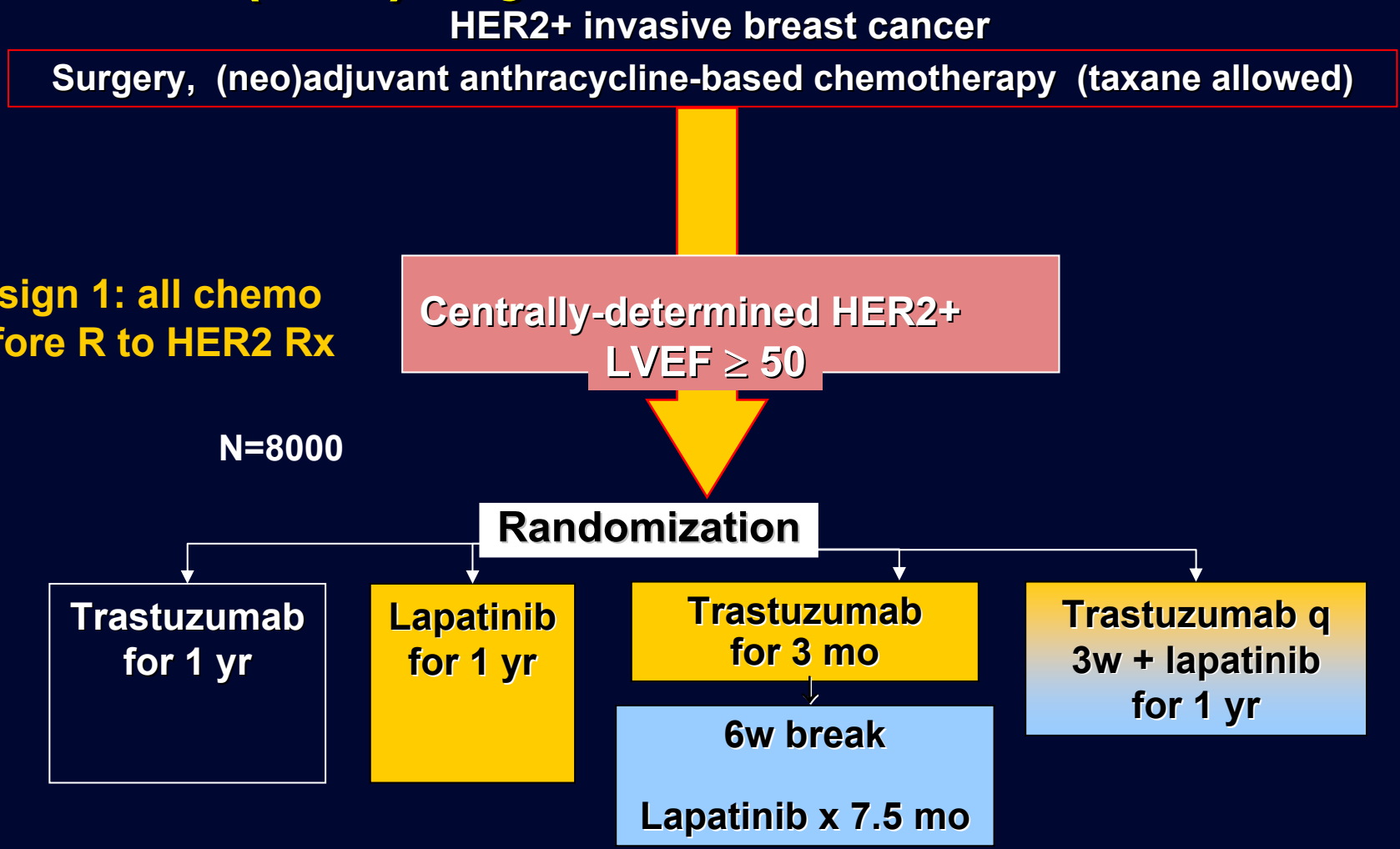
BIG 2.06/NCCTG N063D Phase III HER2+ (neo)Adjuvant Trial - ALTTO



PIs: M Piccart, EA Perez

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Conclusion

- The Mayo PGRN and NCCTG are in the position to conduct clinically relevant and scientifically rigorous research in pharmacogenomics of anti-cancer agents

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